CLAIMS:

1. A method of producing a comminuted suspension of particles, which comprises:

subjecting an initial suspension of particles to a comminution procedure carried out in a sterilised particle size reduction apparatus, said particle size reduction apparatus comprising an interaction chamber for reducing the particle size of the suspension, and an intensifier for introducing the suspension into the interaction chamber at high pressure, and recovering a suspension of particles of reduced size,

characterised in that components of the particle size reduction apparatus are sterilisable and the method includes a sterilisation step in which at least surfaces of the apparatus contacting the suspension are sterilised.

2. A method according to Claim 1, wherein the particle size reduction apparatus is as defined in any of Claims 9 to 19.

3. A method according to Claim 1 or Claim 2, wherein the intensifier comprises a plunger reciprocating within a barrel and an annular high pressure seal as defined in any of Claims 30 to 42.

4. A method according to any preceding claim, wherein the sterilisation step is as defined in any of Claims 43 to 61.

5. A method according to any preceding claim, wherein the sterile suspension comprises Budesonide or Fluticasone.

6. A method according to any preceding claim, wherein particle size is monitored until a final particle size in the suspension of mass median diameter 2-3 μm is obtained.

7. A method according to any preceding claim, further comprising the step of packaging the sterile suspension into sterile ampoules.

8. A nebule containing a sterile suspension prepared according to any of Claims 5 to 7.

9. A sterilisable particle size reduction apparatus, comprising an interaction chamber for reducing the particle size of a suspension, and an intensifier for introducing the suspension into the interaction chamber at high pressure.

10. Apparatus according to Claim 9, wherein the intensifier comprises an output and an input, and the interaction chamber comprises an input and an output, the output of the intensifier being connected to the input of the interaction chamber and the output of the interaction chamber being connected to the input of the intensifier, and wherein there is no conduit between the output of the intensifier and the input of the intensifier other than via the interaction chamber.

11. Apparatus according to Claim 9 or Claim 10, wherein valves in the conduits between the intensifier and the interaction chamber are sterilisable diaphragm needle valves.

12. Apparatus according to any of Claims 9 to 11, wherein the intensifier comprises a bore and a reciprocating plunger and a seal between the

plunger and the bore according to any of Claims 30 to 42.

13. Apparatus according to any of Claims 9 to 12, wherein the intensifier comprises a reciprocating plunger, and a bushing assembly, suitably according to any of Claims 20 to 29, to guide the plunger, wherein the bushing assembly comprises a channel in or on the surface of the bushing assembly to allow steam or water to pass through the bushing assembly whilst the plunger is in place.

14. Apparatus according to any of Claims 9 to 13, wherein the intensifier comprises a plunger connected via a threaded cam nut to a connecting rod, at one end of which connecting rod is a screw thread to receive the cam nut, and wherein the dimensions of the screw thread and the thread of the cam nut are such that as the nut is screwed onto the connecting rod, and wherein respective mating surfaces of the cam nut and the connecting rod mate simultaneously.

15. Apparatus according to any of Claims 9 to 14, comprising a heat exchanger to maintain the temperature of the suspension at from 7°C to 40°C in use.

16. Apparatus according to any of Claims 9 to 15, comprising a pressure relief valve which is a rupture disc.

17. Apparatus according to any of Claims 9 to 16, wherein non-return valves in conduits between the intensifier and the interaction chamber have metal-to-metal seats.

18. Apparatus according to any of Claims 9 to 17, comprising a first heat

exchanger to maintain temperature of the suspension in the interaction chamber and a second heat exchanger to maintain temperature of the suspension in the intensifier, wherein the first and second heat exchangers are independently controlled.

19. Apparatus according to any of Claims 9 to 18, comprising a seal that prevents suspension from reaching the oil that drives the intensifier, for example in the event of failure of a plunger seal in the intensifier.

20. A bushing assembly for use with a cylindrical plunger, comprising a bushing holder and a bushing, held in place by the bushing holder, wherein the bushing assembly comprises one or more conduits to allow passage of sterilising steam or water therethrough.

21. A bushing assembly according to Claim 20 for a plunger that reciprocates in a plunger barrel, comprising a bushing holder which attaches to a neck of the barrel and a bushing held in place by the bushing holder and which guides the plunger into and out of the barrel, wherein the bushing and/or the bushing holder comprises one or more conduits to allow passage of sterilising steam or water through the bushing assembly.

22. A bushing assembly according to Claim 20 or Claim 21, wherein said bushing comprises one or more grooves located on its outer surface.

23. A bushing assembly according to any of Claims 20 to 22, wherein said bushing comprises one or more grooves located on its inner surface.

24. A bushing assembly according to Claim 22 or Claim 23, wherein said

one or more grooves are parallel to the longitudinal axis of the bushing.

25. A bushing assembly according to Claim 22 or Claim 23, wherein said one or more grooves are formed in a spiral around the longitudinal axis of the bushing.

26. A bushing assembly according to any of Claims 20 to 25, wherein the bushing comprises one or more grooves and the bushing holder comprises one or more grooves or one or more conduits to allow passage of sterilising steam or water therethrough.

27. A bushing assembly according to Claim 26, wherein said one or more grooves of said bushing and bushing holder are in alignment.

28. A bushing assembly according to Claim 27, wherein said bushing further comprises one or more projections that cooperate with one or more recesses in said bushing holder in order to align said one or more grooves of said bushing with those of the bushing holder.

29. A bushing assembly according to Claim 27, wherein said bushing holder further comprises one or more projections that cooperate with one or more recesses in the bushing in order to align said one or more grooves of said bushing with those of the bushing holder.

30. An annular high-pressure seal, for a plunger reciprocating within a barrel, comprising lower and upper body portions, said upper portion being in the form of a cup and having sides surrounding a recess, the sides being outwardly deformable so that respective outer and inner edges of the sides of the cup make, in use, sealing contact with

respectively the barrel and the plunger, the seal further comprising a brace to prevent the sides from collapsing into the recess under low pressure and wherein the brace comprises a resilient plastics material.

31. An annular high-pressure seal, for a plunger reciprocating within a barrel, comprising lower and upper body portions, said upper portion being in the form of a cup and having sides surrounding a recess, the sides being outwardly deformable so that respective outer and inner edges of the sides of the cup make, in use, sealing contact with respectively the barrel and the plunger, the seal further comprising a brace to prevent the sides from collapsing into the recess under low pressure and wherein the seal is sterilisable.

32. A plunger seal according to Claim 30 or Claim 31, wherein said brace presents a smooth surface free from cavities.

33. A plunger seal according to any of Claims 30 to 32, wherein said plastics material is disposed in said recess.

34. A plunger seal according to Claim 33, wherein said plastics material fills said recess so that the upper surface of said plastics material is level with or nearly level with the height of said cup sides.

35. A plunger seal according to any of Claims 30 to 34, further comprising a metal spring.

36. A plunger seal according to Claim 35, wherein the metal spring is enclosed within the resilient plastics material of the brace.

37. A plunger seal according to any of Claims 30 to 36, wherein said seal is operable at temperatures up to 75°C.

38. A plunger seal according to any of Claims 30 to 37, wherein said seal is operable at temperatures up to 90°C.

39. A plunger seal according to any of Claims 30 to 38, wherein said seal is operable at temperatures up to 122°C.

40. A plunger seal according to any of Claims 37 to 39, wherein said seal material is virgin PTFE or glass-strengthened PTFE.

41. A plunger seal according to any of Claims 30 to 40, wherein said brace is manufactured from a different material to that of the other seal components.

42. A plunger seal according to Claim 41, wherein the resilient plastics material of the brace is more flexible than the material of the upper and lower body portions of the seal.

43. A method of sterilising a particle size reduction apparatus, comprising charging a non-sterile particle size reduction apparatus according to any of Claims 9 to 19 with steam, to achieve sterilisation.

44. A method according to Claim 43, comprising validating sterilisation according to any of Claims 81 to 83.

45. A method according to Claim 43 or Claim 44, comprising insulating

valves and conduits downstream of the interaction chamber, so as to maintain steam temperature during sterilisation.

46. A method according to any of Claims 43 to 45, comprising:

connecting steam traps to the apparatus;

connecting temperature monitors to the apparatus;

introducing steam into the apparatus;

monitoring temperature at each of the temperature monitors;

noting the time at which temperature recorded by each of the temperature monitors has reached the sterilising temperature;

continuing to introduce steam into the apparatus for a predetermined period.

47. A method according to Claim 46 wherein the period is determined by:

introducing heat-resistant bacterial spores into the apparatus;

introducing steam into the apparatus and monitoring apparatus temperature until it has reached the sterilising temperature;

continuing to introduce steam for a first known amount of time;

determining whether after that first known amount of time sterilisation has been achieved; and

if sterilisation has not been achieved, repeating the method for a second, longer known amount of time.

48. A method according to Claim 47, wherein sterilisation is deemed to have occurred when a six log reduction in heat-resistant bacterial spores has been achieved.

49. A method according to any of Claims 46 to 48, wherein the sterilising temperature is 121°C.

50. A method according to any of Claims 43 to 49, comprising introducing steam into the intensifier and downstream of the interaction chambers.

51. A method according to any of Claims 43 to 50, comprising pre-heating the interaction chambers.

52. A method according to any of Claims 43 to 51, wherein all steam exiting the intensifier passes through the interaction chambers.

53. A method of sterilising a particle size reduction apparatus, comprising charging a non-sterile particle size reduction apparatus according to any of Claims 9 to 19 with pressurised, superheated water so as to sterilise the apparatus.

54. A method according to Claim 53, comprising operating the intensifier so as to control the temperature of the water during sterilisation.

55. A method according to Claim 54, comprising adjusting pressure within the apparatus so as to adjust temperature within the apparatus.

56. A method according to any of Claims 53 to 55, comprising introducing the water into the intensifier and introducing steam into the isolation area of the intensifier, the steam being at the same temperature as or at a higher temperature than the water.

57. A method according to Claim 56, wherein the steam is at least 0.5°C higher than the water.

58. A method according to any of Claims 54 to 57, comprising:

introducing water at a temperature below 100°C into the apparatus; and

operating the apparatus so as to increase the temperature of the water to the sterilising temperature.

59. A method according to Claim 58, wherein the sterilising temperature is 121°C.

60. A method according to any of Claims 53 to 59, comprising flushing the apparatus with sterile air once the apparatus has been sterilised.

61. A method according to any of Claims 53 to 60, wherein the pressurised, superheated water comprises a surfactant.

62. A method of preparing a sterile suspension, comprising:

obtaining a sterile particle size reduction apparatus;

passing a sterile suspension through the sterile apparatus; and

monitoring particle size in the suspension.

63. A method according to Claim 62, wherein the sterile particle size reduction apparatus is obtained according to the method of any of Claims 43 to 61.

64. A method according to Claim 62 or Claim 63, wherein the sterile suspension comprises Budesonide or Fluticasone.

65. A method according to any of Claims 62 to 64, wherein particle size is monitored until a final particle size in the suspension of mass median

diameter 2-3 μm is obtained.

66. A method according to any of Claims 62 to 65, further comprising the step of packaging the sterile suspension into sterile ampoules.

67. A nebule containing a sterile suspension prepared according to any of Claims 62 to 66.

68. A seal retractor, comprising a shaft and at least one projection moveable between a first and a second position;

wherein said first position is for insertion of the seal retractor into a bore containing a seal, and said second position is for removing the seal from the bore.

69. A seal retractor according to Claim 68, wherein in said second position the at least one moveable projection is projected and wherein in said first position the at least one moveable projection is retracted.

70. A seal retractor according to Claim 68 or Claim 69, wherein the seal is an annular seal, and with the projection in said first position the retractor can be inserted through the seal, and with the projection in said second position the retractor can exert a pulling force on the seal.

71. A seal retractor according to Claim 70, wherein in said second position, the at least one moveable projection secures the seal on to the seal retractor.

72. A seal retractor according to Claim 71, wherein in said second position, the at least one moveable projection does not project beyond the lip of

the seal.

73. A seal retractor according to any of Claims 68 to 72, wherein said at least one moveable projection is located at the terminus of the seal retractor.

74. A seal retractor according to Claim 73, wherein said at least one moveable projection is connected to control means to enable remote control of said at least one moveable projection between said first and second positions.

75. A seal retractor according to Claim 74, wherein said control means comprises a rotatable knob and wherein rotating said knob causes the at least one moveable projection to rotate between said first and second positions.

76. A method of accurately positioning a seal into a bore, comprising the steps of:

securing a seal to the seal retractor of any of Claims 68 to 75 with said at least one moveable projection in the second position; and

inserting said seal retractor into said bore; and

thereby accurately positioning the seal into the bore.

77. A method according to Claim 76, further comprising the steps of:

moving said at least one moveable projection to the first position; and

removing the seal retractor from the bore, leaving the seal in situ.

78. A method according to Claim 76 or Claim 77, wherein moving said at least one moveable projection to the first position releases the seal from the seal retractor.

79. A method of removing a seal from a bore, comprising the steps of:

(a) inserting a seal retractor according to any of Claims 68 to 75 into the bore, with the at least one moveable projection in the first position;

(b) moving the projection to the second position and removing the seal retractor from the bore;

thereby removing the seal from the bore.

80. A method according to Claim 79, wherein said method is carried out under sterile conditions.

81. A method of validating sterility of a bore, comprising the steps of:

(a) under sterile conditions, removing a seal from the bore according to the method of Claim 79 or Claim 80;

(b) under sterile conditions, transferring the seal to growth medium; and

(c) observing whether there is growth of microorganisms in the growth medium, thereby determining whether the bore is sterile.

82. A method according to Claim 81, further comprising the initial steps of inoculating a seal with heat-resistant bacterial spores, inserting the seal into the bore, and carrying out a sterilisation method according to any of Claims 43 to 61.

83. A method according to Claim 82, wherein the seal is inoculated with at least $1x10^6$ heat-resistant bacterial spores.